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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/737,457	03/12/97	CARDY	D 960670.ORI

HM12/0613

ORRIN M HAUGEN
HAUGEN AND NIKOLAI
820 INTERNATIONAL CENTRE
900 SECOND AVENUE SOUTH
MINNEAPOLIS MN 55402-3325

EXAMINER	
EWOLDT, G	
ART UNIT	**PAPER NUMBER**
1644	19

DATE MAILED: 06/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/737,457	Applicant(s) Cardy et al.
	Examiner Gerald Ewoldt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Apr 3, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5-12, and 14-24* is/are pending in the application.

Of the above, claim(s) *24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5-12, and 14-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply With Sequence Rule.

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's Amendment, filed 4/3/00 (Paper No. 18) is acknowledged. Claims 1-3, 5-12, and 14-24 are pending.

2. Claims 1-3 and 5-12, and 14-23 are being acted upon. The claimed invention being acted upon is a chimeric polypeptide comprising an anti MHC I or II binding portion, a p53 effector portion, and an HIV tat translocation portion.

3. Claim 24 stands withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. As noted in the previous action, **the peptide sequences on page 11, line 5, page 12, line 1, and page 13, line 10 of the specification must be brought into sequence compliance.**

5. In view of Applicant's amendment and response, filed 4/3/00, only the following rejection remains.

6. Claims 1, 5-11, and 20-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,283,323, of record.

The '323 patent teaches a chimeric polypeptide comprising an immunoglobulin molecule, which itself comprises a binding portion and a translocation portion, and an effector portion. The '323 polypeptide binds a cell surface antigen (an immunoglobulin), induces internalization, and allows the immunogenic peptide to be presented by both MHC Class I and II molecules on the target cell surface so as to modulate immune responses, including CTL and T helper cell responses. The '323 polypeptide is broken down into a number of different peptides which are presented by a number of different MHC haplotypes, depending on the ability of the specific MHC molecule to bind the specific peptides.

7. Applicant's arguments, filed 4/3/00, have been fully considered but have not been found convincing. Applicant argues that the '323 patent does not teach a translocation portion. It is an inherent property of immunoglobulins that they possess a translocation portion as evidenced by DeFranco (1999), who teaches that antigens are taken up by B-cell receptors and on the cell surface and cycled to "internal membrane compartments" (page 246, column 1, paragraph 3).

8. The following are New Grounds of Rejection.

9. Claims 1-3, 5-12 and 14-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

10. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claims 1-3, 5-12 and 14-23 without an undue amount of experimentation. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the broad concept of "modulating the immune response" encompassed by the claims. Applicant discloses that the invention can be used for the treatment of diseases as widely varied as cancer and autoimmune disorders (page 4, second paragraph). The specification, however, fails to provide sufficient guidance regarding the specific embodiments of the invention to be used for the treatment of specific disorders. Applicant provides just two examples of experiments actually performed, both of which provide only *in vitro* ^{51}Cr assay data using transformed cell lines with little relevance to *in vivo* modulation of the immune system. As noted by Derner (1994), "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic studies in the human body." (Page 320, first column, second paragraph. Kahan states that "no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy," (page 558, column 2, first paragraph). It is therefore well established in the art that the actual manipulation or modulation of *in vivo* immune responses is complex, unpredictable, and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Applicant's arguments, filed 4/3/00, have been fully considered but have not been found convincing. Applicant argues that the references cited by the Examiner are "inapposite" because they relate to limitations seen with certain cell lines and immune assays where *in vitro* effects are not always the same as those seen *in vivo*. Applicant further argues that in their case their *in vitro* assays "precisely mimic the mechanisms occurring *in vivo*. Applicant also argues that MHC presentation is required for an *in vivo* effect. While MHC presentation is required and necessary for immune activation, it is not sufficient. MHC presentation is but one component of a multi-step process leading to an immune response. Applicant further fails to explain why the disclosed T-cell and APC clones used in the disclosed assays provide sufficient guidance in the face of cited references to the contrary. It is noted that one of the cell lines used in the disclosed assays (Sp2/0)

is an "ageless" cell line of unknown origin such as is discussed in by Dermer (1994). Finally, Applicant fails to provide guidance as to how the same invention used in the same method of immunomodulation can provide a treatment for conditions requiring both immunostimulation and immunosuppression.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-3, 5-12, and 14-23, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Casten et al. (1988, newly cited) in view of Fawell et al. (1994, of record), and Noguchi et al. (1994, of record).

14. Casten et al. teach a chimeric polypeptide comprising a binding portion comprising at least a portion of an immunoglobulin molecule having specific binding affinity for a eukaryotic target cell surface component (MHC Class I or Class II receptors) and an effector portion consisting of at least one copy of an immunogenic peptide whereby binding of the polypeptide induces internalization to allow presentation of the effector by the MHC of the target cell (see particularly page 173 paragraph 2).

The reference teaching differs from the claimed invention in that it does not teach the use of an HIV tat translocation portion nor does it teach a p53 effector portion.

15. Fawell et al. teach the use of the HIV tat protein for cellular translocation (see particularly page 668, second paragraph). They teach that HIV tat can be used as a "generic" translocation signal to "efficiently deliver heterologous molecules into cells" (page 664, paragraph 3).

Noguchi et al. teach the use of p53 as an "obvious candidate for T cell recognition" because the gene is "frequently mutated in tumors of experimental animals and humans" (see particularly page 3171, first column, second paragraph and pages 3173-3174, **Discussion**).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the antibody-effector chimeric polypeptide, as taught by Casten et al., by the addition of an HIV tat translocation domain, as taught by Fawell et al.,and combine it with a p53 effector portion, as taught by Noguchi et al. One of ordinary skill in the art would have been motivated to refine the internal cellular targeting of the chimeric antibody of Casten et al. with the generic translocation component, as taught by both Fawell et al., "to efficiently deliver heterologous molecules into cells", and modify the effector component to

display various effectors, including p53, because p53 is "frequently mutated in tumors of experimental animals and humans", as taught by Noguchi et al., and is thus an obvious choice as a protein to be presented by MHC for immune system targeting.

Applicant argues that in the previous rejection under 35 U.S.C. 103(a) the Baier et al. (1995) reference that was used was published after the priority date of the instant application and was thus used improperly. The rejection has been withdrawn and a new rejection has been made. Applicant further argues that the combined Fawell et al. and Noguchi et al. references do not make the instant invention obvious. Fawell et al. use the HIV Tat protein to confer cellular translocation on four disparate proteins and further discuss the advantages of the use of HIV Tat for the general delivery of proteins into cells, thus providing motivation for its use as a translocation component in the instant invention. Noguchi et al. teach that p53 is an "obvious candidate" for tumor recognition because of its widespread expression on tumors, thus providing motivation for its use as an effector component in the instant invention.

16. Because of the new rejections this action has not been made final.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
June 5, 2000

Christina Chan
CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP ~~1800~~ 1640

Application No.: 08/737,457

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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